Chapter

Approach and Management of Anaplastic Carcinoma Thyroid

Zuzaki Shabin, R. Rejnish Kumar, Malu Rafi, Lekha M. Nair, John Mathew and Cessal Thommachan Kainickal

Abstract

Anaplastic carcinoma thyroid, also known as undifferentiated thyroid carcinoma, is a rare but highly aggressive malignant tumor, which accounts for 2–3% of all thyroid malignancies. It is mostly seen in elderly females in their 6th or 7th decade. It carries a very bad prognosis with an average median survival of 5 months. Patients often present with a rapidly growing, painful, woody hard lower anterior neck mass fixed to underlying structures. In addition to local invasion, patients also present with regional nodal spread and distant metastasis. Though the risk factors for anaplastic carcinoma thyroid are unknown, most of them develop in the setting of long-standing goiter, possibly in an undiagnosed, well-differentiated thyroid carcinoma. Management of anaplastic carcinoma thyroid demands a multidisciplinary approach with the involvement of surgeon, radiation oncologist, radiologist, and endocrinologist. The conventional treatment of anaplastic carcinoma thyroid includes surgery, radiation, and chemotherapy. Recently, multitarget tyrosine kinase inhibitors are also incorporated into the treatment. However, prognosis of the disease is very poor with 4 months of overall survival of 35% and overall disease-specific mortality of 98–99%. In this chapter, we discuss how to approach the condition and various treatment strategies to provide improved treatment outcomes for patients diagnosed with anaplastic carcinoma thyroid.

Keywords: anaplastic carcinoma thyroid, presentation, investigations, surgery, radiation, chemotherapy, targeted agents

1. Introduction

Anaplastic carcinoma thyroid (ATC) is a rare type of thyroid cancer that carries a worse prognosis. It is extremely aggressive, and the average median survival of ATC is 5 months, with less than 20% of the patients alive after 1 year of diagnosis.

2. Epidemiology and pathogenesis

ATC accounts for 1–2% of all thyroid malignancies. It usually affects patients in their 6th to 7th decade with a female predominance (male/female ratio: 1.5:2) [1–3]. However, it contributes up to 14–50% of the annual mortality associated with thyroid cancer [1]. The age-adjusted annual incidence is one to two per million people [4, 5].

Based on different tumor registries, the frequency of ATC is variable in different countries; however, there has been a drastic reduction in its incidence owing to better dietary iodine intake as well as timely diagnosis and treatment of DTC and MNG [1].

ATC usually originates in the background of a long-standing goiter. Dedifferentiation of differentiated thyroid cancer cells is considered the most common cause of ATC. Dedifferentiation arises due to multiple chromosomal aberrations, alteration in signal transduction pathways, and cell-cycle derangement.

BRAF, RAS oncogene, PIK3CA, PTEN, and TP53 mutations are the most commonly associated genetic alterations in ATC [6, 7]. Reduced levels of E-cadherin and beta-catenin are also associated with ATC [8].

Around 20–30% of patients have coexisting differentiated thyroid cancer with papillary being the most common (20%) [9, 10]. Serial biopsies of the thyroid gland also predispose to ATC [11]. Commonly seen mutations and their expression are listed in **Table 1**.

3. Prognosis

ATC carries a dismal prognosis with mortality approaching 100% with 1- and 5-year survival rate less than 30 and 14%, respectively [17–20]. Patients with localized disease have a better prognosis than those with regional or distant metastasis [9, 20]. Tumor size less than 6 cm in maximum dimension carries a better prognosis [9, 18]. Other favorable prognostic factors include unilateral tumor, localized with node-negative or no extrathyroidal extension [16, 20, 21].

Unfavorable factors include older age at diagnosis, male gender, airway compromise during the presentation, and distant metastasis [16, 20].

Mutations associated with ATC (frequency in %) [8]	Expression
TP53 [12]	Upregulated
CTNNB1 [13]	Upregulated
BRAF [14]	Upregulated
RAS [15]	Upregulated
PI3KCA [16]	Downregulated
PTEN [17]	Downregulated
APC [9]	Downregulated

Table 1.
Most common mutations and their expression associated with ATC.

4. Clinical features

The majority of the patients present with a rapidly progressing neck mass with complaints of dysphagia, dyspnea, and neck pain. Approximately 90% will have regional or distant spread at the time of diagnosis [17–19]. The regional spread shows infiltration of perithyroidal fat, lymph nodes, trachea, esophagus, great vessels of the neck, and mediastinum. Based on the infiltration of adjacent neck structures, patients can also develop hoarseness (recurrent laryngeal nerve invasion), Horner's syndrome (parasympathetic chain involvement), and thromboembolic episodes due to carotid infiltration.

Around 40% of patients present with cervical lymphadenopathy and 43% will have distant metastasis most commonly involving lungs followed by bone and brain [20].

Also, patients can present with constitutional symptoms, such as pyrexia of unknown origin, anorexia, weight loss, and rarely with features of thyroiditis [22, 23].

On examination, there will be bilateral but asymmetric enlargement of the thyroid gland with ill-defined borders. Usually, they are nodular, woody hard in consistency, and may be tender. Some nodules may be fluctuant due to focal tumor necrosis [24]. Due to adhesion with the adjacent structures, most of the time the swelling does not move with swallowing. The skin over the swelling may be erythematous and ulcerated.

During clinical examination, they should undergo an ENT evaluation to rule out vocal cord dysfunction or airway compromise.

Other findings include dilated chest wall veins due to superior vena cava obstruction (SVCO) from a retrosternal thyroid growth, stridor due to tracheal invasion, and vocal cord paralysis.

5. Diagnosis

ATC is a very aggressive tumor with a very short doubling time, and hence disease burden should be assessed accurately and promptly.

Laboratory investigations should include a complete blood count, a baseline evaluation of liver and renal function, thyroid function tests, albumin levels, and serum electrolytes levels. Nutritional assessment is also required as most of them will have dysphagia and reduced food intake.

Fine needle aspiration cytology from the thyroid mass can yield an early diagnosis. Morphologic patterns of ATC include spindle cells, pleomorphic giant cells, and squamoid histologies [16]. Most of them will have a mixed morphology of two or all the three patterns and they show extensive necrosis, atypical mitoses, and numerous mitotic figures. However, for immunostaining and molecular studies, a core biopsy is preferred. Routinely they will not stain positive for TTF1, PAX8, and thyroglobulin. Patterns of IHC in various thyroid malignancies are summarized in **Table 2**.

Poorly differentiated carcinoma, large cell lymphoma, and extension of laryngeal carcinoma are the most common differential diagnosis.

Radiological evaluation should be done immediately without any delay. High-resolution ultrasound can be done as it is convenient, rapid, and easy in assessing tumor extent, neck nodes, and adjacent structure involvement.

IHC	DTC	ATC	MTC	SCC	Lymphoma
Pancytokeratin	+++	+++/−	+++	+++	−
Thyroglobulin	+++	−	−	−	−
TTF-1	+++	−/+	+/−	−	−
BRAF v600E	+/-	−/+	−	−	−
PAX8	+++	+/−	+/−	−	−/+
Ki67	<5%	>30%	<20%	>30%	Variable
Chromogranin	−	−	+++	−	−
Calcitonin	−	−	+++/−	−	−
CEA	−	−	+++	−	−
P53	−	+/−	−	+/−	+/−
CD45	−	−	−	−	+++

Table 2.
Patterns of IHC in various thyroid malignancies [25].

Other imaging modalities include CT/MRI of the neck and chest to assess tumor extent and infiltration to adjacent structures. FDG-PET scan has recently gained a role in imaging ATC as it helps in the accurate diagnosis of distant metastasis compared to other imaging modalities [15]. If trachea or esophagus infiltration is suspected, upper GI endoscopy or bronchoscopy is indicated [20, 25].

Molecular testing can be done if available; however, its clinical utility is not well established. Next-generation sequencing should be performed for targetable mutations under the context of a clinical trial. Rapid testing of BRAF V600E mutation is most commonly done if available in FNA or core needle biopsy specimens.

6. Staging

The American Joint Committee on Cancer (AJCC) 8th edition considers all anaplastic cancers as Stage IV. The T category follows the same definitions as those for differentiated thyroid cancers. Intrathyroidal anaplastic cancers form Stage IVA, whereas gross extrathyroidal extension or nodal metastasis form Stage IVB and distant metastasis form Stage IVC.

7. Treatment approach

Initial therapy in these patients mainly depends on the stage of disease and mutation status. Based on this, various treatment options include surgery, radiation with or without chemotherapy, systemic therapy, and palliation.

Gross resection is the main goal in patients with ATC, but the extent of resection should always outweigh the potentially devastating complications and morbidity of the procedures. Airway assessment and prompt treatment without delay are most important. Securing and maintaining a patent airway is challenging in these patients, but, routine tracheostomy is not recommended as it has not shown any improved outcome in survival or quality of life.

Tracheostomy is recommended in impending airway compromise and in those tumors that will not benefit from debulking.

7.1 Stage IVA

Stage IVa includes disease confined within the thyroid capsule. Around 2–15% of patients present with Stage IVa disease, in which, total thyroidectomy with a therapeutic central and lateral neck node dissection is recommended [25, 26]. Attaining gross negative margins have shown a significantly better prognosis than those with tumor residue ($p < 0.005$) [26]. Sugitani et al. reported that, although the benefit from additional therapies for completely resected Stage IVa ATC was not significant, they tend to show better survival with adjuvant radiation compared to those who underwent radical surgery alone (HR: 0.37; 95% CI: 0.121.13; $p = .081$) [27]. However, for completely resected ATC (R0 resection), additional therapies are not routinely indicated.

7.2 Stage IVB

Around 35% of the patients present as Stage IVb with extrathyroidal extension or cervical nodal involvement. They benefit from a combined modality approach.

For resectable tumors, total thyroidectomy with central and lateral therapeutic neck dissection followed by adjuvant chemoradiation has shown significantly prolonged cancer-specific survival compared to those who underwent surgery alone or with adjuvant RT alone (HR: 0.45; 95% CI: 0.250.81; $p = .0083$) [27].

The intensity-modulated RT technique is recommended to get better dose distribution and reduced toxicities [28]. Several authors have reported a dose–response relationship and showed that a dose of more than 60 Gy has shown a good outcome [14, 29, 30]. Commonly delivered radiation dose includes 70 Gy to the gross tumor or 66–70 Gy to the postoperative bed and 54 Gy to the potential microscopic spread region using a standard fractionation schedule [31, 32].

Several chemotherapy agents are used as concurrent, but mostly Doxorubicin 20 mg/m^2 or Paclitaxel 50 mg/m^2 weekly is given [14, 33, 34].

The role of hyperfractionation is not known, as there is poor evidence to show that it is better than conventional fractionation. Also, hyperfractionation is associated with increased toxicity [31, 35, 36].

However, careful patient selection is required as the procedure has an impact on quality of life. Hence, those who get a meaningful clinical benefit should be offered combined modality treatment. The best outcome is seen when adjuvant radiation is started as early as possible, once the patient has recovered from surgery [37].

For unresectable tumors with BRAF mutation, neoadjuvant treatment with Dabrafenib (150 mg twice daily) and Trametinib (20 mg daily) is started to downsize the tumor to facilitate a complete surgical resection [38, 39]. For poor responders of mutation-directed therapies, palliative radiation is an option.

7.3 Stage IVC

Around 55% of ATC patients present with distant metastasis. Stage IVc has no curative treatment and is fatal. One case series has reported a median survival of 4.2 months in those with distant metastasis at presentation compared to 6 months in

nonmetastatic ATC [34]. Stage IVc is managed with palliative radiation or debulking with or without systemic therapies.

Palliative resection or debulking should be considered to avoid a future or to treat current airway compromise, which may prolong and improve quality of life. As discussed initially, most of the patients are in their 6th or 7th decade. Hence, airway preservation is enough for old age life preservation.

Palliative external beam radiotherapy (EBRT) has a definite role in symptom control for those who have unresectable/metastatic diseases. It helps in reducing the growth of neck mass and thereby alleviates the pressure symptoms. Various schedules are there, but commonly followed ones are 20 Gy in 5 fractions or 30 Gy in 10 fractions.

Systemic therapies include cytotoxic agents, targeted agents, and immunotherapies. If patients have another targetable mutation, such as NTRK, RET fusion, or ALK, they should be enrolled in clinical trials in mutation-directed systemic therapy.

8. Role of cytotoxic therapy

Chemotherapy is an important independent prognostic factor associated with improved survival [13, 40, 41]. However, data on comparing different chemotherapy regimens in these patients are very limited and underpowered due to the low incidence and aggressiveness of the tumor. In the absence of molecular abnormalities, most commonly given chemotherapy includes a combination of Paclitaxel and carboplatin, Cisplatin and Doxorubicin, Docetaxel and Doxorubicin, Paclitaxel alone or Doxorubicin alone [25]. The role of the combination of Cisplatin and Doxorubicin as well as Paclitaxel as a single agent is being studied in ATC and has shown moderate response [19]. However, all these are based on fairly small single studies that need further validation.

ATC has a very rapid doubling time of 3–12 days, hence, some authors recommend that the chemotherapy regimens should be administered in shorter intervals, on weekly basis rather giving every 3–4 weeks [3, 31]. Systemic therapy protocols are listed in **Table 3**.

Treatment	Protocols and dose
Chemotherapy [3]	Doxorubicin (20 mg/m^2) + Cisplatin 120 mg/m^2) every 28 days Paclitaxel (175 mg/m^2) + carboplatin AUC 5 every 21 days Paclitaxel 50–100 mg/m^2 + Carboplatin AUC2 weekly Docetaxel 20 mg/m^2 + Doxorubicin 20 mg/m^2 weekly Paclitaxel alone 30–60 mg/m^2 or Docetaxel 20 mg/m^2 weekly
BRAF and MEK inhibitors [42, 43]	Dabrafenib 150 mg twice daily + Trametinib 2 mg once daily
RET inhibitor [44]	Selpercatinib 160 mg twice daily or 120 mg twice daily (if body weight <50 kg)
NTRK inhibitor [45]	Larotrectinib 100 mg twice daily Entrectinib 600 mg once daily
ALK inhibitor [46]	Crizotinib 250 mg twice daily Larotrectinib 100 mg twice daily

Table 3.
Systemic therapy protocols.

9. Role of targeted agents

Primary chemoresistance is a commonly encountered issue in ATC that often results in a bad prognosis. Hence, newer therapeutic agents are being investigated in ATC, targeting various molecular alterations.

As mentioned above, one-fourth of the ATC is associated with mutation of BRAF and RAS [47]. A phase II trial was conducted in BRAF V600E-positive tumors including 36 patients with ATC, where the patients were treated with the BRAF inhibitor Dabrafenib plus the MEK inhibitor Trametinib. The treatment was well tolerated with an ORR of 56% (95% CI, 38.1–72.1%), with three complete responses and a median PFS and OS of 6.7 and 14.5 months, respectively [42, 43]. The combination was FDA approved in 2018 as 1st line therapy for BRAF V600E-positive ATC patients.

Unfortunately, acquired resistance to BRAF inhibitors due to secondary mutation of MAPK pathway or via PI3K/AKT/mTOR pathway is common in ATC, and hence newer targeted agents are needed. Around 2–3% of ATC patients will have a mutation of NTRK, ALK, or RET fusion.

For such mutation-positive ATC, very high response rates are reported with specific inhibitors in various trials. A pooled subgroup analysis of trials investigating the role of Larotrectinib in ATC showed a response rate of 29% in two out of seven patients [45, 48]. Similarly, long-lasting responses were also noted with Selpercatinib and Crizotinib in RET fusion ATC and ALK-rearranged ATC, respectively [44, 46]. However, these are small studies, some are equivalent to case reports and need more validation.

Inhibitors of PI3K/AKT/mTOR pathway like Everolimus were tested but showed no response [49]. Combination of Sorafenib and Temsirolimus also could not demonstrate a durable response [50].

Though anti-angiogenic agents, such as Lenvatinib, are approved in radioiodine refractory thyroid cancers, their role in ATC is controversial. Based on a single-arm phase II study with 51 ATC patients, Lenvatinib showed a median PFS benefit of 7.4 months, a median OS of 10.6 months, and an ORR of 24% [51]. However, a recent prospective phase II Lenvatinib trial was stopped due to futility as the interim analysis reported a very low response rate (2.9%) and survival outcome [52].

10. Role of immunotherapy

ATC shows high expression of PD-1/PDL-1, and hence immunotherapy may be a promising approach in these patients. However, data available on its use in ATC are limited. Many phase II trials are ongoing with immunotherapy alone as well as in combination with other agents.

The combination of Pembrolizumab and Lenvatinib in ATC is evaluated in the phase II trial of ATLEP (Anaplastic Thyroid Carcinoma Lenvatinib Pembrolizumab) study and has shown a partial response of 37.5% [53]. Also, a single institution study by Lorch et al. has reported partial response in one-third of the ATC patients treated with a combination of Ipilimumab and Nivolumab [54].

Another PD-1 inhibitor Spartalizumab was tested by Capdevila et al. in 41 heavily pretreated ATC patients and showed a response rate of 19.6%. The median OS was 5.9 months with 40% alive at 1 year. The median PFS was 1.7 months. The response rate was higher for those who had a greater PDL-1 expression (35%) [55]. But, the drug is not FDA approved and is not commercially available.

Drug	Study design	Number of ATC patients (among total)	Median OS (months)
Sunitinib [12]	Phase II	4/71	NA
Axitinib [56]	Phase II	2/60	NA
Pazopanib [57]	Phase II	15/15	3.7
Imatinib [58]	Phase II	11/11	NA
Gefitinib [59]	Phase II	5/27	NA
Vemurafenib [60]	Phase II	7/122	NA
Fosbretabulin [61]	Phase II	26/26	4.7
Spartalizumab [55]	Phase II	38/42	5.9
Efatutazone + Paclitaxel [62]	Phase 1	15/15	3.3
Fosbretabulin+ carboplatin+ Paclitaxel [63]	Phase II/III	80/80	5.2

Table 4.
Newer drugs and their clinical trials.

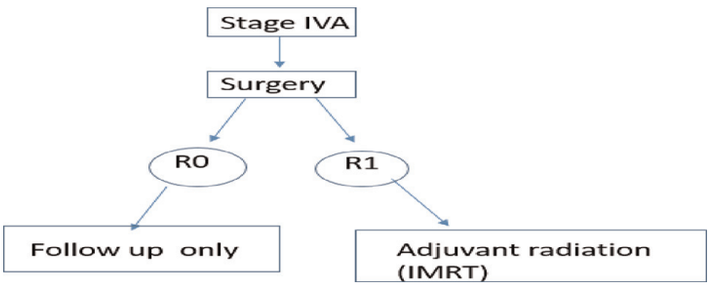

Figure 1.
Stage IVA treatment approach.

Many newer drugs are being tested in phase II and III trials for ATC due to its aggressive nature and poorer outcomes than conventional treatment. A few are listed in **Table 4**.

Stage-wise treatment approach is summarized in **Figures 1–3**. Clinical trials are encouraged and the best supportive care can be considered as an option at any point of treatment.

11. Future directions

Considering the aggressive nature of the disease and its dismal prognosis, novel therapies targeting the signal transduction pathways associated with ATC are to be investigated. Several ongoing trials are being conducted that investigate the role of combining TKIs with immunotherapy or chemotherapy (**Table 5**).

12. End-of-life care

Most of the patients are present in a very advanced stage due to the rapid progression of the disease and will not be eligible for any kind of local or systemic therapy.

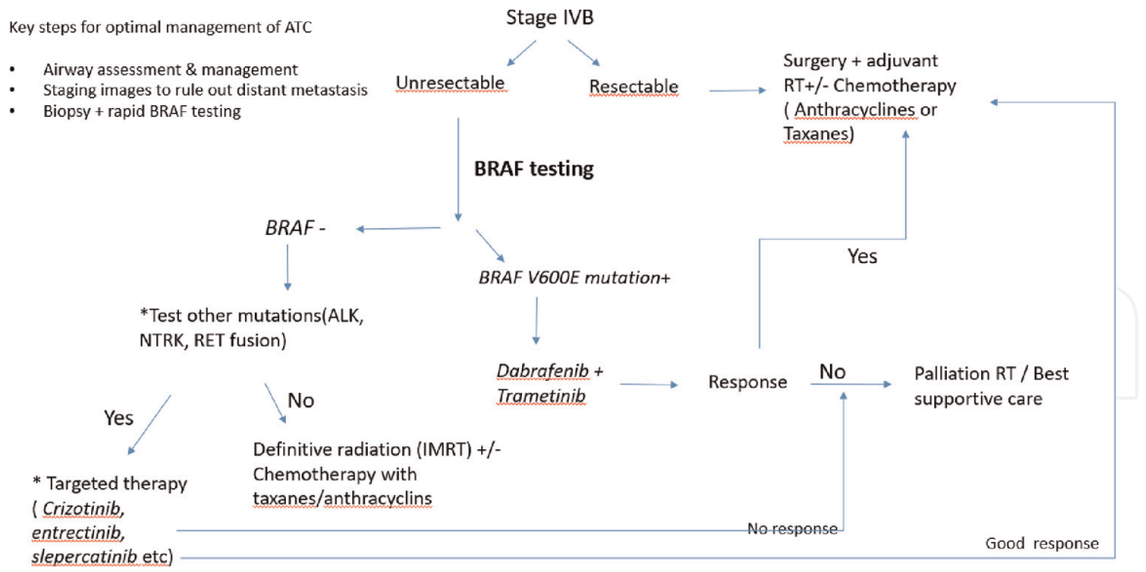

Figure 2.
Stage IVB treatment approach.

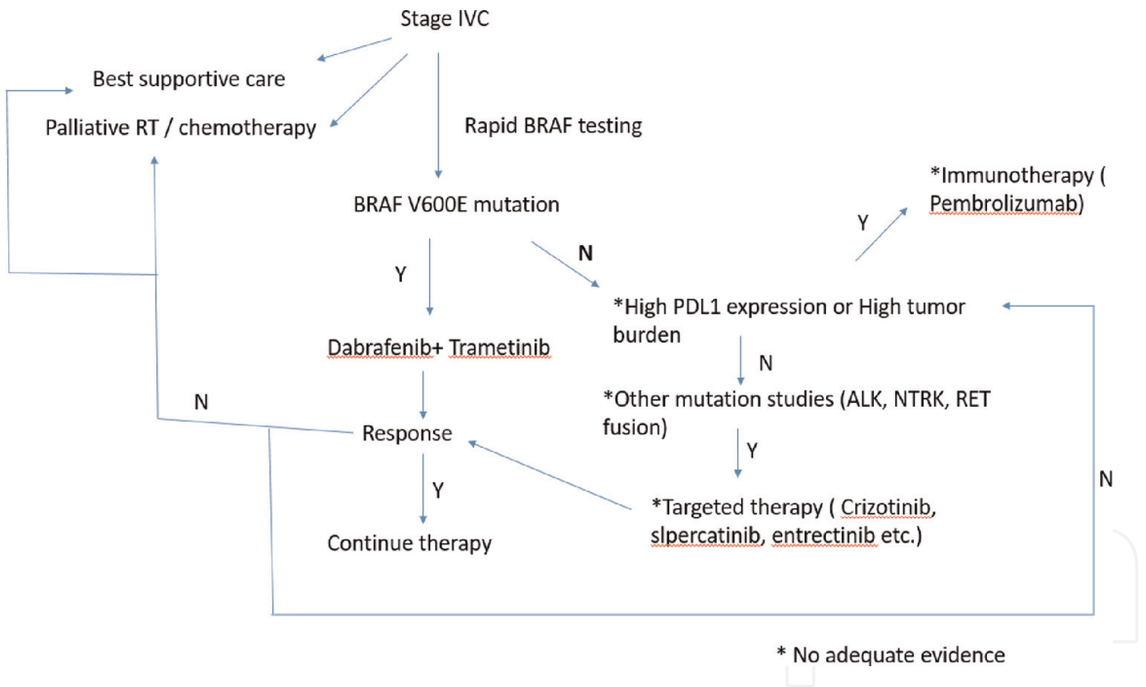

Figure 3.
Stage IV C treatment approach.

End-of-life life care and best supportive care form an integral part of management in these groups of patients [25].

13. Surveillance and follow up

Active surveillance for those who had a complete response to initial treatment is needed. CT of the chest is done within 4 weeks and a single PET–CT is done after 3 months of treatment [15].

Trials	Investigating drug(s)	Phase	Status
NCT03085056 [64]	Trametinib + Paclitaxel in Advanced ATC	Phase 1	Recruiting
NCT02152137 [65]	Efatutazone + Paclitaxel in Advanced ATC	Phase 2	Active, not recruiting
NCT04552769 [66]	Abemaciclib (CDK4/6 inhibitor) in advanced ATC	Phase 2	Recruiting
NCT04675710 [67]	Pembrolizumab + dabrafenib + Trametinib a Neoadjuvant in BRAf mutated ATC	Phase 2	Recruiting
NCT04400474 [68]	Cabozantinib + Atezolizumab in advanced ATC	Phase 2	Recruiting
NCT04579757 [69]	Surufatinib + Tislelizumab in advanced ATC	Phase 1/2	Recruiting
NCT04759911 [70]	Selpercatinib as neoadjuvant in ATC with RET alterations	Phase 2	Recruiting

Table 5.
Ongoing trials in ATC [3].

CT of the neck/chest/abdomen is done thereafter every 1–3 months for the initial 2 years. Later on, less frequent imaging is recommended. Brain imaging is not routinely done, except in case of symptoms of brain metastasis.

There is no role for radioiodine scanning/ablation or serum thyroglobulin measurement.

Thyroid hormone replacement is required for maintaining euthyroid status. T4 should be started (1.6 mcg/kg body weight) immediately after surgery. TSH suppression to less than normal is not indicated in ATC.

14. Conclusion

ATC is a rare thyroid malignancy with an extremely grave prognosis. Diagnosis and treatment should be started quickly and should be based on a multidisciplinary approach, including surgery, radiation, chemotherapy, and targeted agents. Stage IVA tumors should undergo primary surgery with gross-negative margins. For completely resected tumors, there is no role for additional therapies. For resectable stage IVB, surgery followed by adjuvant radiation with or without chemotherapy is recommended. For unresectable tumors, mutation-directed therapies based on BRAF mutation are to be incorporated followed by surgery or radiation. For Stage IVC, palliative treatment is recommended with either palliative radiation or debulking with or without systemic therapies. Although newer mutation-directed therapies are being incorporated into the management of ATC, further validation is needed. The inclusion of novel approaches, such as targeted therapy and immunotherapy either alone or in combination with other modalities, may improve outcomes in these patients.

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Author details

Zuzaki Shabin, R. Rejnish Kumar, Malu Rafi,
Lekha M. Nair, John Mathew and Cessal Thommachan Kainickal*
Department of Radiation Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India

*Address all correspondence to: drcessalthomas@gmail.com

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